PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/000752	01.03.2005	01.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D277/56, C07D307/68, C07D213/73, C07D333/38, C07D207/34, C07D233/90, C07D487/04, C07D417/12,

Applicant
SPIROGEN LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Helps, I

Telephone No. +49 89 2399-8209

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000752

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 25(part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 25(part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6-26
	No:	Claims	1-5
Inventive step (IS)	Yes:	Claims	6-26
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-24, 26
	No:	Claims	25 see below

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

V. CITATIONS AND EXPLANATIONS

The following documents are mentioned in this Written Opinion

Tetrahedron, vol.31, p.2936-9 (1975) (A)
Journal of Medicinal Chemistry,
vol.45, p.4443-59 (2002) (B)
Journal of the American Chemical Society,
vol.76, p.4543-5 (1954) (C)
Bioorganic and Medicinal Chemistry Letters,
vol. 7, p.1595-1600 (1997) (D)
Journal of Medicinal Chemistry,
vol.39, p.217-23 (1996) (E)
WO-A-99 46244 (F)
US-A-2002 123634 (G)
Journal of the American Chemical Society,
vol.124, p.10676-82 (2002) (H)
Chemical European Journal, vol.9,
p.2110-2 (2003) (I)
Bioorganic and Medicinal Chemistry Letters,
vol.13, p.2277-80 (2003) (J)

Document (A) discloses the methyl ester of 5-(3-aminophenyl)-furan-2-carboxylic acid (see table, compound 41), and also the corresponding 4-aminophenyl derivative (compound 31). These compounds are novel destroying for claim 1 in which A is a furan ring and B is a phenyl ring, with Z' being a methyl ester group and Z being H. Claim 2 is also not novel because compound 31 is not disclaimed. Claim 3 is also not novel because the compounds of (A) do not fall under the scope of the disclaimers. Claim 4 is also not novel because methyl esters fall under the definition "protected hydroxyl" as given on page 9 of the description. Claim 5 is also not novel because the biaryl compounds of (A) comprise a phenylene and a C5 arylene.

Document (B) discloses 5-(3-aminophenyl)-4-oxalylamino-thiophene-2-carboxylic acid (see table 2, compound 8l. This compound is prepared from the corresponding methyl ester

(see Scheme 1, compound 7l) and 5-(3-aminophenyl)-3-amino-thiophene-2-carboxylic acid methyl ester (Scheme 1, compound 6l). These compounds are novelty destroying for claim 1 in which B is phenylene, A is thiophene, Z' is OH or OCH3, and Z is H. Claims 3 to 5 are also not novel for reasons given above.

Document (C) discloses 4'-amino-3-biphenylcarboxylic acid and 4'-amino-2-biphenylcarboxylic acid (see page 4544, column 1). These compounds are novelty destroying for claim 1 in which A and B are phenylene, Z and Z' are H. Claims 2, 3 and 5 are also not novel for reasons given above.

Document (D) discloses the NH-Boc and NH-SO2CH3 protected derivatives of 3'-amino-biphenyl-3-carboxylic acid and 5-(3'-aminophenyl)-furan-2-carboxylic acid as intermediates for the preparation of amides incorporating aminoalkylborate esters (see Scheme 1, compound 30 and Table 2). These compounds are novelty destroying for claim 1 in which A is phenyl or furyl, B is phenyl, Z is H, Boc, or SO2CH3, and Z' is OH. Claims 2-3 and 5 are also rendered not novel for reasons given above.

Document (E) discloses the t-butyl ester of 4'-amino-biphenyl-3-carboxylc acid (see Scheme 1, reaction (d), first step). This compound is novelty destroying for claim 1 in which A and b are phenylene, Z' is O-t-butyl, and Z is H. Claims 2-5 are also rendered not novel for reasons given above.

Document (F) discloses 5-(4-aminophenyl)-3-oxalylamino-thiophene-2-carboxylic acid (see compound 37) and the corresponding 5-(3-aminophenyl) derivative (compound 35). These compounds are novelty destroying for claim 1 in which A is thiophene, B is phenylene, Z' is OH and Z is H. Claims 2, 3 and 5 are also rendered not novel for reasons given above.

Claims 1 to 5 therefore do not meet the Novelty requirements of Article 33(2) PCT.

The novel structural feature of claim 6 is the presence of a biarylene unit (II) moiety represented by CO-A-B-NH in the polyamide. The dependent claims 7 to 21, as well as claim 22 drawn to compounds of claim 6 for use in therapy, claim 23 drawn to pharmaceutical compositions containing compounds of claim 6, claim 24 drawn to the use of compounds of claim 6 for the preparation of medicaments, ad claim 25 drawn to

methods of treatment using compounds of claim 1 are novel by consequence.

The novel feature of claim 26 is the use of compounds of claims 1-5 as intermediates for the preparation of polyamido compounds of claim 6.

Claims 6 to 21 therefore meet the Novelty requirements of Article 33(2) PCT.

Document (G) describes some pyrrole-amide oligomers and their binding to the DNA minor groove. Also described are benzimidazoles which are substituted by amidinophenyl-furyl moieties (see compounds DB75, DB270 and DB293). Document (H) describes pyrrole polyamides which bind to the hairpin region of DNA. In document (I) it is shown that these polyamides can also incorporate a 2-(aminopyrrolyl)-benzimidazole-6-carboxylic acid moiety. Document (J) describes the pyrrolo[2,1-c][1,4] benzodiazepine moiety which is used as an end group in the compounds of claim 11, and their interaction in the minor groove of DNA. However, in none of these documents is a suggestion given to the skilled man that the poylamide compounds of the present application which incorporate biaryl moieties of formula (II) would act as DNA minor groove binders and hence be useful for the treatment of proliferative diseases. Inventive step (Article 33(3) PCT) can be recognised for claims 6 to 26 because the problem of providing further DNA minor groove binding compounds has been solved in a non obvious manner by these compounds.

For the assessment of the present claim 25 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VII. CERTAIN DEFECTS IN THE INTERNATIONAL APPLICATION

In order to meet the requirements of Rule 5.1(a)(ii) PCT, documents (A)-(F) should be identified in the description and the relevant prior art disclosed therein should be briefly discussed.

VIII. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION.

in view of the scope of claim 1 in which A and B are defined as "optionally substituted C5-6 arylene", which appears to include any 5 or 6 membered aryl or heteroaryl ring, which may bear any substituent, it was not possible to carry out a complete search for the claimed subject matter within a reasonable time limit. The search was therefore concentrated on compounds including aryl and heteroaryl rings as disclosed in the examples, according to the Guidelines, B-III, 3.7.